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The Association of Depression, Anxiety and Nocturia: A Systematic Review

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Abstract

Purpose—This systematic review focuses on the relationship between nocturia and depression/anxiety. Our objective is to provide an overview of current data on the epidemiology, pathophysiology and patient management implications of the association between nocturia and depression/anxiety.

Materials and Methods—We queried PubMed®, Web of Science® and Embase™ in July 2012 to identify abstracts, and original, review and editorial articles on nocturia and mood disorders, specifically depression and anxiety. The search was done using the key words “nocturia,” “depression” and “anxiety.” We complied with the Assessment of Multiple Systemic Reviews (AMSTAR) instrument. We retrieved a total of 500 records, including 95, 81 and 324 from PubMed, Web of Science and Embase, respectively.

Results—Cross-sectional (level 3) data indicated that nocturia and depression/anxiety are strongly associated. One prospective study contended that depression leads to nocturia in a unidirectional relationship. Nocturia poses a greater risk for depression in men vs women. Results conflict on the effect of serotonin reuptake inhibitors on nocturia.

Conclusions—The results of this systematic review suggest a bidirectional association between depression and nocturia. The relationship between anxiety and nocturia is less clear. Practicing clinicians should consider administering a brief self-administered scale to assess for depression in patients with nocturia.

Keywords

urinary bladder; nocturia; depression; anxiety; questionnaires

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Bothersome nocturia decreases quality of life and can lead to embarrassment, social anxiety and/or poor self-esteem.¹⁻³ Nocturia is frequently associated with daytime drowsiness, inability to concentrate, decreased motivation to perform activities and poor self-rated health.^{1,3,4} All of these consequences could place one at increased risk for depression. On the other hand, depressed patients may report increased bother from urinary symptoms due to the tendency of depressed patients to catastrophize symptoms.⁵ Depression may also pose an impediment to effective treatment, ie individuals who are depressed may be less prone to seek out or be compliant with therapy.⁶ Improved understanding of the epidemiological and pathophysiological relationship between nocturia and depression/anxiety, and provider awareness could lead to improved nocturia prevention, detection and treatment.

A systematic review of the relationship between depression/anxiety disorders and nocturia is needed. We provide a comprehensive summary of contemporary published reports on nocturia and depression/anxiety to improve disease understanding and provide a framework for future investigation.

SEARCH METHODS AND EVIDENCE ACQUISITION

Our research question and inclusion criteria were established a priori. PubMed, Web of Science and Embase were queried in July 2012 to identify abstracts, and original, review and editorial articles on nocturia, depression and anxiety. We supplemented our search by seeking expert opinion and reviewing the references in the studies that we included. Gray literature, such as meeting abstracts, were searched for and reviewed. We enlisted the assistance of a reference librarian to produce our search. The search was done using the key words “nocturia,” “depression” and “anxiety.” MeSH® and nonMeSH terms were used. Abbreviations (“LUTS” and “BPH”) were also used. Searches were limited to articles on adults published in English. Studies specifically focused on other lower urinary tract symptoms, such as incontinence, were excluded from consideration. Studies focused on a health condition and depression or nocturia alone were also excluded, eg fatigue, sleep and nocturnal complaints in patients with amyotrophic lateral sclerosis. Due to the heterogeneous nature of the studies included, we did not perform a meta-analysis. Review articles containing distinct information on nocturia and depression or anxiety were included. We complied with the AMSTAR instrument checklist.⁷ The AMSTAR instrument consists of 11 items and is valid for assessing the methodological quality of systemic reviews. Three of us (BNB, AWS and SDB) independently performed study selection and data extraction. If disagreement occurred, a consensus was reached by the abstractors by reviewing and discussing the article or data.

We retrieved a total of 500 records, including 95, 81 and 324 from PubMed, Web of Science and Embase, respectively. We excluded 141 duplicate references, 284 nonEnglish or irrelevant references, eg related to children or incontinence, 45 citations related to medical/neurological conditions and nocturia, and reviews with only a cursory mention of nocturia and depression/anxiety, and 13 citations without direct measures of an association between depression/anxiety and nocturia, and abstracts corresponding to already included studies. Upon a review of the literature 7 articles were added and deemed pertinent (see

supplementary references, <http://www.urology.ucsf.edu/node/831>). Level of evidence was assessed by 4 of us (BNB, AWS, BAE and RCR) using the International Consultation of Urological Diseases grading scale.⁸ When there was disagreement regarding the level of evidence, the investigators discussed the study in question and came to a majority consensus. We detected no conflict of interest in the included studies.

NOCTURIA AND DEPRESSION/ANXIETY RELATIONSHIP

In several large-scale, observational studies groups analyzed the association of nocturia and depression^{1,2,4,9-15} but fewer have examined the association between nocturia and anxiety or a more general designation of mental health^{16,17} (see table). All analyzed studies were cross-sectional^{1,4,9-17} except a prospective cohort study.² Some groups considered nocturia as the outcome,^{1,2,9-11,14,17} while others evaluated depression as a potential outcome of nocturia.^{4,12,13,15,16} Most studies used a single item question to evaluate nocturia frequency^{2,9-12,14,16,17} and a minority used multiple questions.^{1,4,13,15} When modeling nocturia as the outcome, 2 or greater events per night were considered positive in most series.^{1,9,11,14,17} Various validated mental health measures were used with different standard cutoff points to quantify depression and anxiety, including the Center for Epidemiological Studies Depression Scale (CES-D),^{4,13,15} Patient Health Questionnaire-9 (PHQ-9),¹⁴ Geriatric Depression Scale (GDS),¹² and Hospitalization Anxiety and Depression Scale (HADS).^{16,17} Existing studies were heterogeneous with respect to inclusion criteria/stratification (gender^{2,10} and age^{10,12,14}), study population (clinic convenience sample,^{12,17} regional,^{4,13} national¹⁴ or international⁹) and data source (in person interview,^{4,10,13,14} or computer assisted self-administered^{16,17} or self-administered^{1,2,9,11,12,15} questionnaire).

Overall, nocturia increased the odds of reporting depression (OR 1.2–20.24), while depression similarly increased the odds of reporting the outcome of nocturia (OR 1.2–7.73). The study with the highest level of evidence was from Finland.² The group prospectively collected incident cases of nocturia and depressive symptoms to help determine a causal direction for the relationship between nocturia and depressive symptoms. A cohort of 1,580 men 50 to 70 years old was studied during a 5-year period. A single item question on the number of nocturia events and the 5-item Mental Health Inventory were used to define nocturia and depressive symptoms, respectively. Nocturia at baseline had no significant effect on the odds of depressive symptoms during followup. However, a dose-response relationship was found between depressive symptom severity at study entry and incident cases of moderate or severe nocturia. Antidepressant or antipsychotic medications did not appear to increase the nocturia incident rate. The investigators did not state whether the use of lithium to treat bipolar disease, which can lead to diabetes insipidus, resulted in nocturia. Based on these findings, they proposed a unidirectional effect of depressive symptoms on the incidence of moderate or severe nocturia. Furthermore, they stated that depressive symptoms that are untreated may lead to nocturia.

Three of the other studies were from Sweden.^{9,11} In a cross-sectional self-administered survey of 1,948 men and women 20 to 64 years old participants who urinated 2 more times per night had increased odds of reporting poor mental health based on a single item question (OR 1.9, 95% CI 1.2–3.0).⁹ The single item mental health question was “My mental health

is: very good/rather good/rather poor/very poor.” A dose-response relationship was identified between increasing nocturia frequency and worsening mental health. These researchers also surveyed a separate population of 1,375 men and women to examine depression with the Major Depression Inventory.¹¹ The odds of major depression in men with nocturia 2 or more times per night was almost twice that of women with nocturia (OR 6.5, 95% CI 2.6–15.6 vs 2.8, 95% CI 1.3–6.3). In another report based on this population, these investigators found that using selective SSRIs doubled the risk of reporting 2 or greater nocturia events after adjustment for depression and age.¹⁸ Whether SSRI use has a pathophysiological role in the development of nocturia in depressed patients is unclear. Antidepressant use has not been shown to affect the day-to-night urine production ratio.¹⁹

Two cross-sectional studies from the United States demonstrated an association of nocturia with an increased risk of depression. In a convenience sample of 547 male clinic patients Johnson et al noted a significantly greater risk of depression in those with 3 or more nocturia events.¹² In the Boston Area Community Health (BACH) Survey Kupelian et al observed that the risk of depression symptoms in patients with nocturia was almost 3 times higher in men with vs without nocturia and almost twice as high in women (OR 2.79, 95% CI 1.81–4.31 and 1.80, 95% CI 1.29–2.51, respectively).^{4,13} In a separate cross-sectional, questionnaire based study of 2,042 women nocturia was the only urinary symptom significantly associated with depression on multivariate analysis.¹⁵

Based on cross-sectional (level 3) and minimal prospective (level 2) data, depression and nocturia appear to be frequently comorbid. The strongest prospective study contends that depression leads to nocturia in a unidirectional relationship.² Limited data exist that depression may predispose men to nocturia. It is tempting to speculate that the sleep disturbances that accompany depressive symptoms may predispose men to urinate during the sleep period since they are more often awake and, as a result, may urinate more frequently than men with polyuria or abnormal bladder capacity as a cause of nocturia.¹¹ Nocturia appears to carry a greater risk of depression in men than in women.^{11,13} Results conflict in regard to the effect of SSRIs on nocturia.

PATIENT TREATMENT IMPLICATIONS

Understanding that nocturia and depression are frequently comorbid can have important implications for the treating clinician. Steers et al recommended that clinicians use a brief self-administered scale, such as the HADS, to assess for anxiety and depression in all new patients.²⁰ Patients who screen positive for a mental health disorder may be more anxious about a diagnostic test such as cystoscopy or require more counseling before surgery. Having insight into the patient emotional state may promote improved communication and prevent patient dissatisfaction with treatment. In addition, patients who screen positive for mental health disorders may benefit from referral to an appropriate provider, eg psychologist, social worker or psychiatrist. The response to medical management for nocturia may be improved by also treating the underlying mood disorder.

FUTURE DIRECTIONS

The results of this systematic review suggest a bidirectional association of depression and anxiety with nocturia. However, many evaluated studies relied on a single survey instrument, failed to note longitudinal changes and lacked evidence of causality. Moreover, the degree to which mood disorders influence therapy for nocturia and vice versa is under studied. This represents a fertile ground for further evaluation. Data on longitudinal cohorts could also help determine the impact of de novo nocturia and depression on individuals with existing depression and nocturia, respectively. The potentially mediating role of sleep disturbance or undiagnosed sleep disorders must be further evaluated. Lastly, although many potential mechanisms underlying the association of depression and anxiety with nocturia have been postulated, robust data on pathophysiological mechanisms are sparse. Further study is needed to help identify patients at risk and develop novel therapeutic strategies.

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Abbreviations and Acronyms

SSRI serotonin reuptake inhibitor

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Evidence of association between nocturia and depression in population based studies

References	Evidence Level	No. Pts/No. Women	Mean Age (range)	Study Design	Assessment (No. questions)	Depression Measure	Outcome	Association
Asplund et al ¹¹	3	1,375/766	Not available	Cross-sectional, self-administered, mailed	No. nocturia episodes/night (1)	Major Depression Inventory	Nocturia 2 or greater	Men OR 6.5 (95% CI 2.6–15.6), women OR 2.8 (95% CI 1.3–6.3)
Asplund et al ⁹	3	1,948/1,019	Not available	Cross-sectional, self-administered, mailed	No. nocturia episodes/night (1)	1 Item mental health question	Nocturia 2 or greater	OR 1.9 (95% CI 1.2–3.0)
Asplund et al ⁹	3	1,375/766	Not available	Cross-sectional, self-administered, mailed	No. nocturia episodes/night (1)	Major Depression Inventory	Nocturia 2 or greater	Predictor major depression yes vs no OR 4.6 (95% CI 2.8–7.5) + SSRI treatment yes vs no OR 2.2 (95% CI 1.1–4.5)
Coyne et al ¹⁶	3	30,000/15,861	Not available	Cross-sectional, self-administered, internet	No. nocturia episodes/night (1)	HADS-A + D	HADS-A + D 8 or greater	No risk estimate, nocturia associated with anxiety in men + women, not depression
Gourova et al ¹⁰	3	2,934/0	Not available (55–75)	Secondary data review from screening questionnaire	No. nocturia episodes/night (1)	Single item question on depression	Nocturia 3 or greater	Univariate OR 1.0 (95% CI 1.42–2.54)
Häkkinen et al ²	2	1,633/0	58.4 (not available)	Prospective, self-administered, mailed	No. nocturia episodes/night (1)	5-Item Mental Health Inventory	Nocturia nonmild (0–2), moderate (3–4), severe (5+)	Men with mild/moderate depression/moderate/severe nocturia RR 3.0 (95% CI 1.6–5.7) + moderate/

References	Evidence Level	No. Pts/No. Women	Mean Age (range)	Study Design	Assessment (No. questions)	Depression Measure	Outcome	Association
Hashim et al ¹⁷	3	30,000/15,860	Not available	Cross-sectional, self-administered, internet	No. nocturia episodes/night (1)	HADS-A + D	Nocturia 2 or greater	severe depression-model severe depression-model severe depression-model severe depression-model severe depression-model severe depression-model severe depression-model
van der Vaart et al ¹⁵	3	3,200/3,200	Not available (20–70)	Cross-sectional, self-administered, mailed	Frequent nighttime urination yes/no (1), bother degree (1)	CES-D	CES-D 16 or greater	No risk estimate, nocturia associated with high HADS-A + D
Johnson et al ¹²	3	547/0	58.1 (40+)	Cross-section, self-administered in clinic	No. nocturia episodes/night (1)	GDS short version	GDS greater than 5	Nocturia5+/ night OR 6.5 (95% CI 2.1– 20.24)
Kupelian et al ⁴	3	5,503/3,202	Not available (30–79)	Cross-sectional, in person interview	Nocturia (3)	CES-D	CES-D 5 or greater symptoms	Symptoms greater than 1 yr increasing OR 1.73 (1.2–2.3)
Kupelian et al ¹³	3	5,503/3,202	Not available (30–79)	Cross-sectional, in person interview	Nocturia (3)	CES-D	CES-D 5 or greater	Odds of depression with 3+ voids/night men OR 2.68 (95% CI 1.45–4.93), women OR 2.63 (95% CI 1.6–4.32)

References	Evidence Level	No. Pts/No. Women	Mean Age (range)	Study Design	Assessment (No. questions)	Depression Measure	Outcome	Association
Markland et al ¹⁴	3	4,163/0	Not available (40+)	Cross-sectional, in person interview	No. nocturia episodes/night (1)	PHQ-9	Nocturia 2 or greater	OR 2.5 (95% CI 1.5–3.9)
Tikkinen et al ¹	3	3,307/1,713	Not available (18–79)	Cross-sectional, self-administered, mailed	Nocturia frequency (2)	Antidepressant use yes/no	Nocturia 2 or greater	OR 3.16 (95% CI 1.29–7.73)

Breyer et al.